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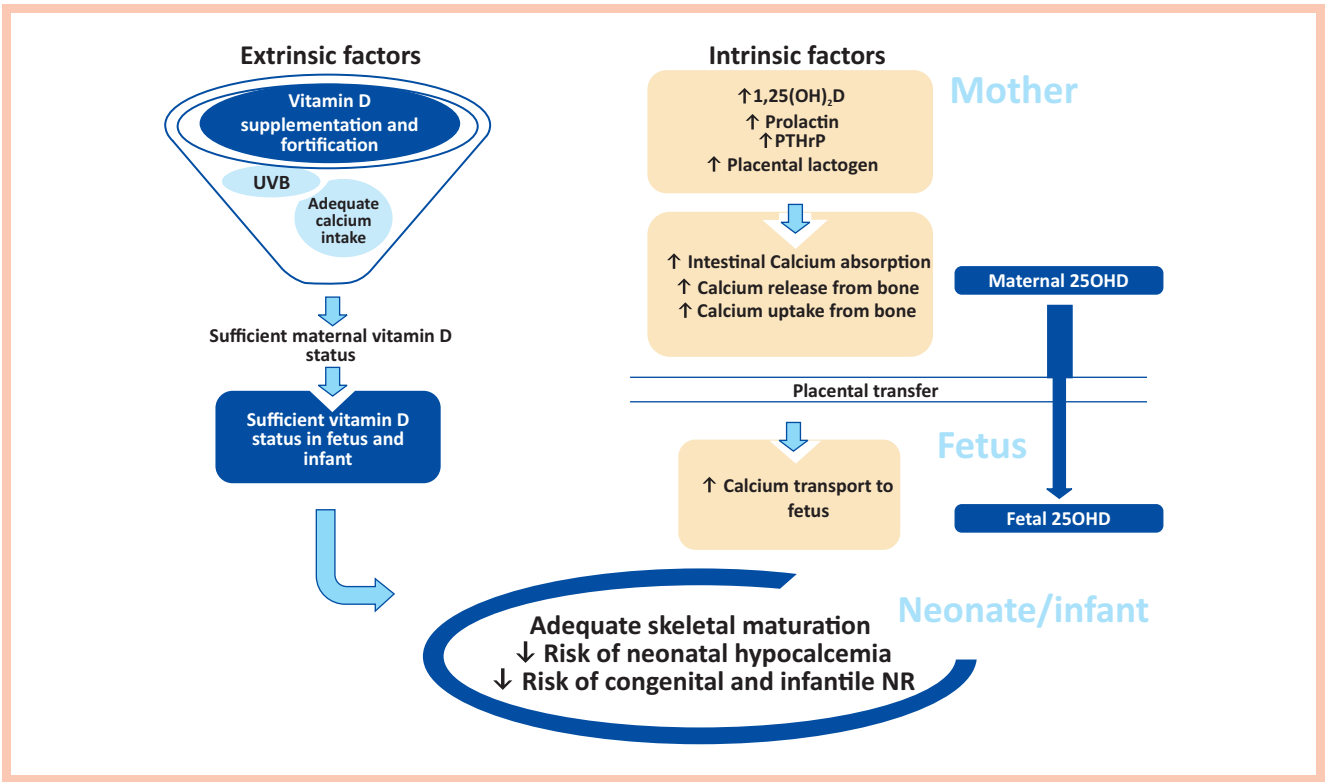
Medical Bulletin

MATERNAL VITAMIN D STATUS, FETAL GROWTH PATTERNS, AND ADVERSE PREGNANCY OUTCOMES

Vitamin D (VD), a fat-soluble vitamin, has a variety of functions that are important for growth and development, including regulation of cell differentiation and apoptosis, immune system development, and brain development.

Pre-pregnancy or peri-pregnancy Vitamin D deficiency (VDD) in the mother can have important ramifications for the fetus and infant. Low vitamin D status during pregnancy is common & is a major public health concern. Reports of high prevalence of VDD below 25 nmol/L in pregnant women ranges between 60-80%. As such, VD status during pregnancy is critical for maternal health, fetal skeletal growth, and optimal pregnancy outcome, as inadequate maternal vitamin D status has been associated with adverse pregnancy outcomes for both the mother and infant. Studies have confirmed that adverse pregnancy outcomes, such as preeclampsia, low birth weight, neonatal hypocalcemia, poor postnatal growth, skeletal fragility, and increased incidence of autoimmune diseases, can be associated with low VD levels during pregnancy and infancy.



Vitamin D plays important roles beginning early in pregnancy and is required for immune cell function during the processes of implantation and placental formation. Vitamin D has been positively associated with the production of vascular endothelial growth factor and placental growth factor, both pro-angiogenic factors that regulate early vascularization of the placenta. In addition, vitamin D plays essential roles in bone health and formation, and maternal vitamin D status has been associated with fetal skeletal development and birth weight.

First trimester maternal vitamin D status was positively associated with fetal linear growth patterns from the second trimester to birth & hence first trimester (or preconception to increase first trimester vitamin D status) may represent a critical time point for intervention in females with deficiency. The Endocrine Society vitamin D guidelines for pregnant women, concluded that there may be “important potential benefit” of vitamin D supplementation on risk for small for gestational age (SGA) and preterm birth.

The relationship between early pregnancy vitamin D status and fetal growth patterns for length and birth outcomes may be explained by multiple mechanisms. Vitamin D has been associated with placental angiogenesis, in which higher 25(OH)D has been related to higher production of pro-angiogenic proteins and lower production of antiangiogenic proteins regulating the formation of the vascular network within the placenta early in pregnancy.

The disruption of these processes through insufficient vitamin D bioavailability could adversely impact implantation and placental development early in gestation, in turn impacting later fetal growth. Fetal 25(OH)D concentrations closely mirror maternal 25(OH)D, and thus, maternal deficiency will be reflected in suboptimal bioavailability of 25(OH)D in the fetus to support skeletal growth, which begins between the sixth and seventh weeks of embryonic development. Vitamin D plays an important immunomodulatory role in placental-decidual function, and its role in anti-inflammatory pathways may help to decrease the incidence of infections, one of the most common causes for preterm delivery.

In conclusion, first trimester maternal vitamin D status was positively associated with fetal linear growth patterns. Low first trimester vitamin D status was associated with a higher risk for preterm birth and with a shorter mean length of gestation. Second trimester vitamin D status was not associated with fetal growth patterns or pregnancy outcomes. The first trimester (or preconception to increase first trimester vitamin D status) may represent a critical time point for intervention in females with deficiency however future research is warranted to understand the influence of timing of vitamin D supplementation, including in the preconception period.

The American College of Obstetrics and Gynecologists (ACOG), National Institute for Health and Care Excellence (NICE), and Institute of Medicine (IOM), recommend supplementation in pregnancy. Basis there is a global consensus which recommends that all pregnant women should receive 600 IU/day of supplemental vitamin D to prevent both neonate and infant adverse outcomes. There is international consensus regarding the vitamin D supplementation of breastfed infants. The global consensus guidelines have strongly recommended that all infants, regardless of their mode of feeding, be supplemented with 400 IU/day from birth until 12 months of age based on high-quality evidence

Source: *C. Beck et al. The American Journal of Clinical Nutrition 121 (2025) 376–384; Zhang, H, et.al; Nutrients 2022, 14, 4230. Fiscaletti et al. Public Health Reviews (2017) 38:19*

PLEIOTROPIC EFFECT OF TENELIGLIPTIN ON hs-CRP AND CARDIORENAL PARAMETERS

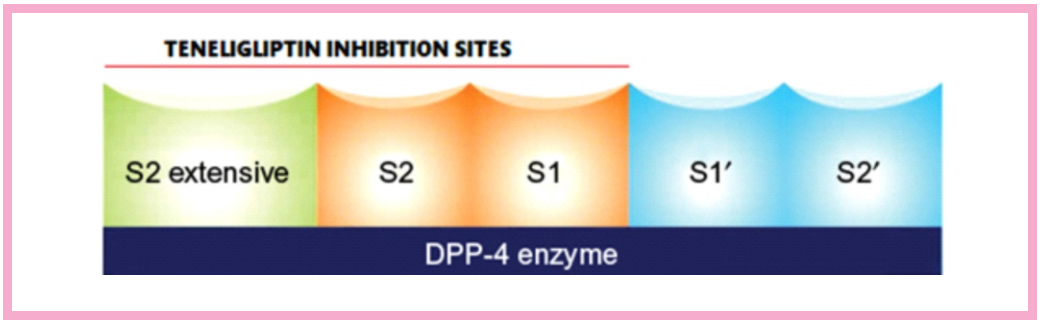
Diabetes mellitus is a chronic metabolic disorder characterized by inappropriately high glucose concentrations in the blood. The prevalence of diabetes is rising annually at a higher rate, and in India 134 million people are expected to get diabetes mellitus by 2045.

Diabetes Mellitus and related complications contributed to approximately 3.1% of total deaths in India as of the year 2016. Persistently elevated blood glucose levels over time cause irreversible damage to blood vessels in the heart, kidney, retina, and nerves, which present as micro and macrovascular complications. Cardiovascular (CV) problems affect up to 80% of persons with type 2 diabetes, accounting for around 65% of deaths in this population. Furthermore, CV problems occur one to two decades sooner in diabetes compared to nondiabetes populations.

In recent decades, “chronic low-grade systemic inflammation,” also known as “meta-inflammation,” has been recognized as an accelerating pathogenic mechanism behind the initiation and progression of diabetes-related complications. hs-CRP is a high sensitivity C-reactive protein assay with a sensitivity range of 0.01–10 mg/L. Such high-sensitivity assays will help in detecting chronic low-grade systemic inflammation, and various studies have concluded that hs-CRP can be an independent predictor of CV diseases (CVDs).

hs-CRP is a principal biomarker of chronic low-grade systemic inflammation and plays a vital role in atherosclerotic plaque formation along with low-density lipoprotein cholesterol. Therefore, it can serve as a surrogate marker for the prediction of CVD risk in type 2 diabetes patients.

Teneligliptin, which is classified as peptidomimetic, has a unique structure having five consecutive rings. Due to this unique structure, teneligliptin acts on S2 extensive subsite of dipeptidyl peptidase (DPP-4); this interaction enhances its potency and selectivity. Teneligliptin has a favorable (J-Shaped) structure leading to small loss of energy during the binding with DPP-4. Once-a-day administration with maximum inhibition of DPP-4 enzyme within 2 hours and >50% inhibition has been noted at 24 hours; no drug–drug interaction and elimination by renal and hepatic route are some of the important clinically significant properties of teneligliptin.



From the various clinical studies, at end of 12-weeks therapy with teneligliptin, resulted in a significant decrease in the hs-CRP levels. The results were consistent across subgroups of participants with statins and without statins treatment in the teneligliptin arm alone, and this confirms the pleiotropic effect of teneligliptin on hs-CRP. Improvement in glycemic control and insulin sensitivity might be one of the possible mechanisms behind the pleiotropic effects of teneligliptin on hs-CRP.

Additionally, there are some signals of possible pleiotropic benefits of teneligliptin in terms of improvement in vascular endothelial function, body weight, and lipid levels.

Teneligliptin causes a modest decrease in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) & the possible mechanism behind this effect could be an improvement in insulin sensitivity, suppression of sympathetic activity, and natriuretic action of incretins. Similarly teneligliptin's potential mode of action for its reno-protective properties has been suggested as oxidative stress attenuation. It has demonstrated reduction in the levels of urinary liver fatty acid-binding protein (Urinary L-FABP) suggesting it's antioxidative and renoprotective pleiotropic actions.

Hyperglycemia is known to induce oxidative stress via activation of the polyol, hexosamine, protein kinase C, and advanced glycation end-product pathways, leading to vascular endothelial dysfunction. Studies have demonstrated significant lowering of HbA1c and LDL-cholesterol levels in the teneligliptin group & possibly this amelioration of glucose and lipid metabolism in this group contributed to improved vascular endothelial function. There are evidences that teneligliptin appears to have multifaceted effects on endothelial function, via its antioxidant capabilities, anti-inflammatory properties, antiplatelet activity, and hydroxyl-radical (OH) scavenging properties due to its structure.

Several clinical studies have demonstrated that teneligliptin, can improve endothelial function and reduce renal and vascular oxidative stress in patients with type 2 diabetes and chronic kidney disease (CKD), independently of reducing albuminuria or improving glucose control. Thus, these potential pleiotropic effects of teneligliptin may be beneficial in T2DM patients for preventing the cardiorenal complications, however larger trials are warranted to corroborate these beneficial effects.

Source: *Kanimozhi, et al.: Perspectives in Clinical Research, Volume 16, Issue 1, January-March 2025*

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